Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

September 29, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 00D-0186; International Conference on Harmonisation; Draft Guidance on M4 Common Technical Document; Quality Part B; Federal Register, August 24, 2000 (fr24au00-90)

Dear Sir/Madam:

Eli Lilly and Company is pleased to have the opportunity to comment on the Quality (Part B) portion of the subject guidance. As a sponsor of many new product applications, Eli Lilly has a long standing interest in and a great deal of experience with the preparation of applications to global regulatory authorities. Lilly shares in the intent to reduce the time and resources used to compile applications, ease the preparation of electronic submissions, facilitate regulatory reviews, and facilitate communication with the agency. In that spirit we offer our general and specific comments on the draft guidance:

GENERAL COMMENTS:

- Our expectations are very high for the Common Technical Document to evolve into a truly harmonized document. While we believe the available draft guidance is a good start, the stated intent will clearly not be met without significant improvements. We fully expect that regional differences will disappear in the future, and that this is actively being addressed.

- We expect that the FDA (along with authorities in other ICH regions) will consider that this guidance represents the ceiling (with respect to requirements) and not a baseline document (i.e. minimum requirements).

00D-0186

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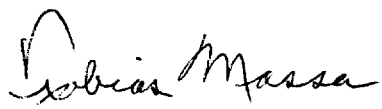
- The level of descriptions in the TOC range from very short and cryptic to excessive details. In some cases there is extensive detail in the QOS and no detail in the TOC. We suggest that changes are made to appropriately balance the information between these areas.

- A discrete definition of biotech products needs to be provided. It needs to be clarified whether in fact vaccines and blood products are excluded.

Detailed specific comments on the proposed guidance are attached.

Sincerely,



Tobias Massa, Ph.D.
Executive Director, Global Regulatory Affairs

Lilly Response to
The Common Technical Document for the Registration of Pharmaceuticals for Human Use - Quality (20 July 2000)

Reference	Issue	Change to	Rationale
Quality Overall Summary (QOS)			
S 3	The QOS should summarize the data on actual and potential impurities…	Replace "potential" impurities with "identified" impurities	
S 3	… (for biotech: product-related and process-related impurities)…	Why is this singled out for biotech, since it applies to both NCE and biotech?	
Table of Contents			
S 2.2	Misspelling in Biotech section—hqytyyarvest(s)	harvest(s)	---
S 2.4	**Critical Steps:** Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled.	Delete the phrase "including experimental data"	Unnecessary regulatory burden to provide details of all experimental data.
S 2.4	**Intermediates:** Specifications and analytical procedures, if any, for intermediates isolated during the process.	Change to **Intermediates:** Specifications and the types of analytical procedures, if any, for intermediates isolated during the process.	It is sufficient to provide the type of methodology used. Unnecessary regulatory burden to provide details of analytical procedures.
S 2.5	The terms "validation" and "evaluation" need to be clearly defined.	---	The term "validation" in the US is construed as GMP validation, whereas in the EU this is construed as process verification.

Reference	Issue	Change to	Rationale
S 3.2	Impurities no detail is provided for this section.	Excerpt discussion of impurities from the Quality Overall Summary	Clarification of requirements.
S 4.4	Define "origin"	Is "origin" equivalent to the site of manufacture?	Clarification of requirements.
S 4	Order of section S 4	Suggest that the order of Section S 4 should be 4.1 Specification, 4.2 Justification of Specification, 4.3 Batch Analyses, 4.4 Analytical Procedures, and 4.5 Validation of Analytical Procedures	Flow of information is clearer.
S 7.1	Stability Summary and Conclusions	Clarify that this is a textual summary.	Clarification of requirements.
S 7.2	Stability Data	Clarify that this is graphical and tabular data.	Clarification of requirements.
P 3.1	Manufacturer(s)	Provide a more precise definition (and examples) of manufacturer (with worldwide applicability). As an example, is the EC release facility required?	Clarification of requirements.
P 3.4	**Critical Steps:** Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled.	Delete the phrase "including experimental data"	Unnecessary regulatory burden to provide details of all experimental data.

Reference	Issue	Change to	Rationale
P 3.4	**Intermediates:** Specifications and analytical procedures, if any, for intermediates including validation of analytical procedures, where appropriate	Change to **Intermediates:** Specifications and the types of analytical procedures, if any, for intermediates ...	It is sufficient to provide the type of methodology used. Unnecessary regulatory burden to provide details of analytical procedures and validation.
P 4	Order of section P 4	Suggest that the order of Section P 4 should be 4.1 Specifications, 4.2 Justification of Specifications, 4.3 Analytical Procedures, and 4.4 Validation of Analytical Procedures	Flow of information is clearer.
P 5	Order of section P 5	Suggest that the order of Section P 5 should be 5.1 Specification, 5.2 Justification of Specification, 5.3 Batch Analyses, 5.4 Analytical Procedures, and 5.5 Validation of Analytical Procedures	Flow of information is clearer.
A 1	Requirement for diagram and facility information	Should not be a requirement since the information is GMP-oriented	Unnecessary regulatory burden to provide diagram and facility information. This information is available for inspections.
A 2	Viral Safety Validation	Include Q5D and Q6B in reference section.	Items are mentioned in text.
-----	Sterilization Validation	Where should Sterilization Validation details reside? Is a Sterilization Validation Package still a US requirement?	Clarification of requirements.

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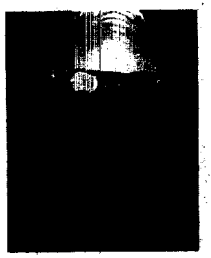

Karl-Heinz "Flete" Klenz – Specializing in the 10[illegible]ke and 100-meter/200-meter freestyle, Klenz is training for a spot on the German National Swim Team for the 2000 Olympic Games in Sydney, Australia[illegible]d at UPS for three years and is currently a part-time preloader in Leipzig, Germany. He is a member of the global UPS Athlete Training Assistance Program (ATAP), which provides employee-athletes with the support they need to pursue their Olympic dreams.